

### **REMARKS**

Following entry of the foregoing amendments, claims 1-19, 21-26, and 28-39 constitute the pending claims in the present application. Claims 21-26 and 28-33 are withdrawn. Claims 20 and 27 are cancelled. Claims 36-39 are new.

#### **Amendments and New Claims**

Applicants have amended claims 1 and 3-4 to recite that the compounds therein are linear polymers. Support for this amendment can be found throughout the specification as originally filed, for example, on page 2, lines 17-20.

Applicants have amended claim 1 to recite that P either “comprises cyclodextrin moieties alternating with linker moieties in the polymer chain or n is at least 1, wherein at least one linker moiety includes a therapeutic agent.” Similarly, Applicants have amended claim 34 to recite that the polymer comprises cyclodextrin moieties alternating with linker moieties in the polymer chain and that the bioactive moieties are attached to the polymer through the linker moieties. Support for these amendments can be found throughout the specification as originally filed, for example, on page 2, lines 18-20; page 3, lines 12-14; and page 16, lines 1-4. Accordingly, claims 5-6 and 10 have been amended to correct antecedence.

Claim 4 has been amended to incorporate subject matter from claims 12 and 35.

Additionally, Applicants have amended claim 8 for clarity and claims 10, 12, and 34-35 to correct matters of form.

Applicants have added new claims 36-37, for which support can be found throughout the specification as originally filed, for example, on page 2, lines 20-23.

Applicants have also added new claim 38, for which support can be found throughout the specification as originally filed, for example, on page 9, lines 7-8.

Applicants have also added new claim 39. Claim 39 corresponds to original claim 1 with subject matter incorporated from claims 12 and 35.

Applicants have also amended the specification to correct a typographical error regarding the structure of  $\beta$ -cyclodextrin on page 38 of the application as originally filed.

Applicants assert the present amendments and newly added claims present no new matter. Applicants reserve the right to pursue subject matter analogous to that in original claims 1, 3-4, and 34 in one or more divisional and/or continuation applications.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1. Elections/Restrictions

Applicants acknowledge the finality of the prior Restriction Requirement. However, Applicants restate that pursuant to MPEP 821.04, in cases where claims to a product and a process for making or using the product are presented in the same application, if one or more claims directed to the product are elected and subsequently found allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product claim must be rejoined. Accordingly, present claim 21 drawn to a process/method of using the product of claims 1-4 should be rejoined on indication of allowance of any of the claims from which it depends.

2. Claim Rejections – 35 USC 112, Second Paragraph

Claims 20 and 27 are rejected under 35 USC 112, second paragraph, as allegedly being vague and indefinite. While Applicants disagree with the Office, without addressing the merits of the rejection, Applicants have cancelled claims 20 and 27 in order to advance prosecution. Applicants reserve the right to pursue subject matter analogous to that in claims 20 and 27 in one or more divisional and/or continuation applications.

3. Claim Rejections – 35 USC 102(b) over WO 00/01734 to Gonzalez et al.

Claims 1-5, 7, 10-18, 20, 27, and 34-35 stand rejected under 35 USC 102(b) as allegedly being anticipated by WO 00/01734 to Gonzalez et al. (“Gonzalez”). Applicants traverse the rejection to the extent that it is maintained over the claims as amended. Since claims 20 and 27 have been cancelled, the rejection is rendered moot for these claims.

According to the Office, Gonzalez discloses linear cyclodextrin (CD) copolymers including an embodiment wherein a folic acid moiety is covalently attached to a copolymer. The Office considers that “ligands” in the art and “therapeutic agents” of the claims are not mutually

exclusive. The Office further considers that the folic acid moiety is described in Gonzalez as a ligand “similar to the ‘targeting ligands’ in the instant invention” and that the folic acid moiety “is also consistent with Applicant’s definition of therapeutic agent.”

Nevertheless, Applicants assert that Gonzalez does not teach or suggest all the limitations of claims 1-4 and 34 as currently amended. In particular, regarding claim 1, Gonzalez does not teach or suggest a polymeric compound comprising cyclodextrin moieties alternating with linker moieties in the polymer chain ... wherein at least one linker moiety includes a therapeutic agent. Similarly, for claim 34, Gonzalez does not teach or suggest a polymer comprising cyclodextrin moieties alternating with linker moieties in the polymer chain, wherein a plurality of bioactive moieties are covalently attached to the polymer through attachments to the linker moieties. Without conceding that folic acid is a therapeutic agent, Applicants note that the folic acid embodiments of Gonzalez (Examples 17 and 18) relate to a cyclodextrin polymer wherein the folic acid group is attached to the polymer via a linker that is *not* part of the polymer chain.

Regarding claim 3, Applicants note that Gonzalez does not teach or suggest linear polymeric compounds with the particular structure of Formula II recited therein, *i.e.*, polymers with one or more cyclodextrin groups not part of the polymer chain.

Regarding claim 4, Applicants highlight that Gonzalez does not teach or suggest linear polymeric compounds with the particular structure of Formula III recited therein, *i.e.*, wherein L<sub>4</sub> is attached to at least one D and/or L<sub>7</sub> is attached to at least one T’.

Since a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference (see MPEP 2131, quoting *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)), Gonzalez does not anticipate claims 1, 3-4, or 34 or claims 2, 5, 7, 10-18, or 35, which are dependent thereon. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

4. Claim Rejections – 35 USC 102(b) over US 6,048,736 to Kosak

Claims 1-20, 27, and 35 stand rejected under 35 USC 102(b) as allegedly being anticipated by US 6,048,736 to Kosak (“Kosak”). Applicants traverse the rejection to the extent

that it is maintained over the claims as amended. Since claims 20 and 27 have been cancelled, the rejection is rendered moot for these claims.

According to the Office, Kosak discloses an aqueous solution comprising a CD polymer covalently attached to gamma globulin via an amide linkage. The Office further states that gamma globulin is described as a targeting ligand and that gamma globulin has known therapeutic activity.

Nevertheless, Applicants assert that Kosak, like Gonzalez, does not teach or suggest all the limitations of claims 1 and 3-4 as currently amended. In particular, Kosak does not teach or suggest linear polymers. The CD polymers of Kosak are cross-linked (see column 7, lines 53-58), for example, by epichlorohydrin (see, for example, Preparation I) or by 1,4-butanediol diglycidyl ether (see, for example, Preparations II-IV, VI). This unselective cross-linking by reaction of the many hydroxyl moieties of CD monomers with cross-linking agents affords a random three-dimensional polymer, not a linear polymer as presently claimed. The three-dimensional facet of the Kosak polymers is a key feature used in physically entrapping therapeutic agents (see column 8, lines 9-11 of Kosak). As such, Kosak does not teach or suggest all the limitations of claims 1 and 3-4, and this reference cannot be said to anticipate claims 1 and 3-4 or claims 2, 5-19, or 35, which are dependent thereon. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

5. Claim Rejections – 35 USC 102(b) over Hristova-Kazmierski

Claims 3-5, 7, 10-16, 19-20, 27 and 35 stand rejected under 35 USC 102(b) as allegedly being anticipated by Hristova-Kazmierski et al. *Bio. Med. Chem. Lett.* **1993**, 3, 831-834 (“Hristova”). Applicants traverse the rejection to the extent that it is maintained over the claims as amended. Since claims 20 and 27 have been cancelled, the rejection is rendered moot for these claims.

The Office notes that Hristova “discloses a  $\delta$  opioid agonist [conjugated] to [a] cyclodextrin.” However, Applicants submit that Hristova does not teach or suggest all the limitations of claims 3-4 as currently amended. Notably, Hristova does not teach or suggest a linear *polymeric* compound such as those depicted in Formulas II and III of claims 3 and 4, respectively. Since Hristova does not teach or suggest all the limitations of claims 3-4, this

reference cannot be said to anticipate claims 3-4 or claims 5, 7, 10-16, 19, or 35, which are dependent thereon. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

6. Claim Rejections – 35 USC 102(b) over Minami

Claims 3-5, 7, 10-16, 19-20, 27 and 35 stand rejected under 35 USC 102(b) as allegedly being anticipated by Minami et al. *J. Pharm. Sci.* **1998**, 87, 715-720 (“Minami”). Applicants traverse the rejection to the extent that it is maintained over the claims as amended. Since claims 20 and 27 have been cancelled, the rejection is rendered moot for these claims.

The Office contends that Minami “discloses biphenyl acetic acid conjugated to a cyclodextrin” (emphasis added). However, Applicants submit that Minami, like Hristova, does not teach or suggest all the limitations of claims 3-4 as currently amended. Notably, Minami does not teach or suggest a linear *polymeric* compound such as those depicted in Formulas II and III of claims 3 and 4, respectively. Since Minami does not teach or suggest all the limitations of claims 3-4, this reference cannot be said to anticipate claims 3-4 or claims 5, 7, 10-16, 19, or 35, which are dependent thereon. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

7. Claim Rejections – 35 USC 102(b) over Yano

Claims 3-5, 7, 10-16, 19-20, 27 and 35 stand rejected under 35 USC 102(b) as allegedly being anticipated by Yano et al. *J. Pharm. Sci.* **2001**, 90, 493-503 (“Yano”). Applicants traverse the rejection to the extent that it is maintained over the claims as amended. Since claims 20 and 27 have been cancelled, the rejection is rendered moot for these claims.

The Office contends that Yano “discloses prednisolone conjugated to a cyclodextrin” (emphasis added). However, Applicants submit that Yano, like Hristova, does not teach or suggest all the limitations of claims 3-4 as currently amended. Notably, Yano does not teach or suggest a linear *polymeric* compound such as those depicted in Formulas II and III of claims 3 and 4, respectively. Since Yano does not teach or suggest all the limitations of claims 3-4, this reference cannot be said to anticipate claims 3-4 or claims 5, 7, 10-16, 19, or 35, which are dependent thereon. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

8. Claim Rejections – 35 USC 102(b) over US 5,183,883 to Tanaka et al.

Claims 3-5, 7, 10-16, 19-20, 27 and 35 stand rejected under 35 USC 102(b) as allegedly being anticipated by US 5,183,883 to Tanaka et al. (“Tanaka”). Applicants traverse the rejection to the extent that it is maintained over the claims as amended. Since claims 20 and 27 have been cancelled, the rejection is rendered moot for these claims.

The Office considers Tanaka to disclose a conjugate of doxorubicin and cyclodextrin. However, Applicants submit that Tanaka, like Hristova, does not teach or suggest all the limitations of claims 3-4 as currently amended. Notably, Tanaka does not teach or suggest a linear *polymeric* compound such as those depicted in Formulas II and III of claims 3 and 4, respectively. Since Tanaka does not teach or suggest all the limitations of claims 3-4, this reference cannot be said to anticipate claims 3-4 or claims 5, 7, 10-16, 19, or 35, which are dependent thereon. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

9. Claim Rejections – 35 USC 103(a) over US 6,048,736 to Kosak

Claims 1-20, 27, and 35 stand rejected under 35 USC 103(a) as allegedly being obvious in view of Kosak. Applicants traverse the rejection to the extent that it is maintained over the claims as amended. Since claims 20 and 27 have been cancelled, the rejection is rendered moot for these claims.

Pursuant to MPEP 2142:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicants' disclosure. *In re Vaack*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants highlight that Kosak teaches cross-linked polymers having random three-dimensional networks. Such cross-linked polymers are critical to accomplish “complete physical entrapment” of therapeutic agents by the polymer (see column 8, lines 9-23). The skilled artisan would have had no motivation to modify the random CD polymers of Kosak to

arrive at the linear polymers presently claimed since such a modification would run contrary to the teachings that the Kosak polymers be able to completely entrap an active agent. The “teaching, suggestion or motivation [to combine teachings must be] found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art” (MPEP 2143.01), and no such motivation can be found in this case. Moreover, “[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).” (MPEP 2143.01). The teachings of *In re Gordon* apply in this situation since modification of the teachings of Kosak to arrive at the linear polymers presently claimed would render the Kosak invention unsuitable for its intended purpose of completely enclosing therapeutic agents therein. As such, there is no motivation to modify the Kosak invention to arrive at that presently claimed.

Analogously, one of skill in the art would not have had a reasonable expectation of success in modifying the Kosak invention to arrive at the presently claimed linear polymers since linear polymers are incapable of complete physical entrapment, as defined in Kosak, of therapeutic agents therein. Without the cross-linked polymeric system of Kosak, therapeutic agents would be free to diffuse out and away from any linear polymer. Accordingly, there is no expectation of success in modifying the Kosak invention to arrive at that presently claimed.

Furthermore, Kosak fails to teach or suggest all the elements of the present claims and does not teach or suggest linear polymers as presently claimed.

For the reasons presented above, Applicants assert that *none* of the requirements for establishing a *prima facie* case of obviousness have been met. Accordingly, Applicants request reconsideration and withdrawal of the obviousness rejection of claims 1 and 3-4 and claims 2, 5-19 or 35, which are dependent thereon.

10. Claim Rejections – 35 USC 103(a) over WO 00/01734 to Gonzalez et al.

Claims 1-5, 7, 10-20, 27, and 34-35 stand rejected under 35 USC 103(a) as allegedly being obvious in view of Gonzalez. Applicants traverse the rejection to the extent that it is maintained over the claims as amended. The Office has rejected claims 1-5, 7, 10-20, 27, and 34-35 over Gonzalez but only presented arguments pertaining to claim 34. Regardless,

Applicants' response is applicable to all the claims rejected as being obvious in view of Gonzalez. Since claims 20 and 27 have been cancelled, the rejection is rendered moot for these claims.

As presented above, Gonzalez does not teach or suggest all the features of the present claims. Pursuant to MPEP 2142, "[t]o establish a prima facie case of obviousness...the prior art reference (or references when combined) must teach or suggest all the claim limitations." *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The Office's contentions that Gonzalez may disclose a polymer comprising a plurality of folic acid moieties and that a "product having non-identical ligands would also be considered a product having both a ligand and a therapeutic agent because both of these agents have both activities" do not overcome the reference's inability to teach or suggest all the features of the present claims. Consequently, the present claims are non-obvious over Gonzalez, and Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 3-4, and 34 and claims 2, 5, 7, 10-19, and 35, which are dependent thereon.

11. Claim Rejections – Obviousness-Type Double Patenting over US 6,884,789 and US 6,509,323

Claims 1-7, 10-15, 20, 27, and 34 stand rejected under the judicially created doctrine of obviousness-type double patenting over claim 7 of US 6,884,789 ("the '789 patent") and over claim 4 of US 6,509,323 ("the '323 patent"). Applicants traverse the rejection to the extent that it is maintained over the claims as amended. Since claims 20 and 27 have been cancelled, the rejection is rendered moot for these claims.

The Office contends that the CD polymers recited in claim 7 of the '789 patent and claim 4 of the '323 patent require the covalent attachment of a targeting ligand and that targeting ligands and therapeutic agents are overlapping. Nevertheless, Applicants assert that claim 7 of the '789 patent and claim 4 of '323 patent do not render obvious claims 1, 3-4, and 34 as currently amended.

As noted in MPEP 804, "the analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 USC 103 obviousness determination." Moreover, Applicants remind the Examiner that the specifications of the '789 and '323 patents



may not be relied upon when conducting the obviousness-type double patenting analysis: “When considering whether the invention defined in a claim of an application would have been an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art. *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1279, 23 USPQ2d 1839, 1846 (Fed. Cir. 1992).” (MPEP 804).

In the present case, claim 7 of the ‘789 patent recites: “The copolymer of claim 1, further comprising wherein at least one ligand is bound to the linear cyclodextrin copolymer; wherein said ligand allows the copolymer to target and bind to a cell.” Claim 4 of the ‘323 patent recites: “A composition of claim 1, wherein at least one ligand is bound to at least one of said water-soluble, linear cyclodextrin copolymer or said water-soluble, linear oxidized cyclodextrin copolymer to target and bind to a cell.” Applicants assert that claim 7 of the ‘789 patent and claim 4 of the ‘323 patent do not teach or suggest all the features of present claims 1 or 34. In particular, claim 7 of the ‘789 patent and claim 4 of the ‘323 patent do not teach or suggest that “at least one linker moiety includes a therapeutic agent” as recited in present claim 1. Furthermore, claim 7 of the ‘789 patent and claim 4 of the ‘323 patent also do not teach or suggest that “a plurality of bioactive moieties are covalently attached to the polymer through attachments to the linker moieties” as recited in present claim 34. Moreover, no motivation exists to make such modifications to claim 7 of the ‘789 patent or to claim 4 of the ‘323 patent to arrive at present claims 1 to 34.

Regarding present claims 3 and 4, claim 7 of the ‘789 patent and claim 4 of the ‘323 patent clearly fail to teach the structure of the polymeric compounds recited in Formula II of claim 3 or Formula III of claim 4. Additionally, no motivation exists for modifying the structure of the polymer of claim 7 of the ‘789 patent or of claim 4 of the ‘323 patent to arrive at the polymers claimed in claims 3 or 4.

As such, with no motivation provided to make modifications to claim 7 of the ‘789 patent or to claim 4 of the ‘323 patent to arrive at instant claims 1, 3-4, or 34 and failure by claim 7 of the ‘789 patent and claim 4 of the ‘323 patent to teach all the features of present claims 1, 3-4, and 34, a *prima facie* case of obviousness-type double patenting has not been established. Accordingly, Applicants request reconsideration and withdrawal of the

obviousness-type double patenting rejection of claims 1, 3-4, and 34 and claims 2, 5-7, 10-15, 20, and 27, which are dependent thereon.

*Applicants Request Inclusion of References Cited on Form PTO-892*

Applicants note that Gonzalez and Kosak, which were used as the basis for some rejections in the outstanding Office Action, were not included in the accompanying Notice of References Cited (Form PTO-892). Applicants are including these references in a Supplemental Information Disclosure Statement filed herewith. Applicants respectfully request the Examiner list any newly cited art on corresponding PTO-892 forms to ensure that such art is printed on any patent which may issue from the pending application (MPEP 707.05(c) and 1302.12).

**CONCLUSION**

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to Deposit Account No. 18-1945, under Order No. ITI-P01-008, from which the undersigned is authorized to draw.

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Respectfully submitted,

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